PROFESSIONAL INFORMATION FOR XIFAXAN

SCHEDULING STATUS

S4

APPROVED
Responsible Pharmacist EQUITY
Sign: ..... Date: 14 July 2020

1. NAME OF THE MEDICINE

XIFAXAN

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 550 mg rifaximin.

For full list of excipients, see section 6.1

Sugar free.

3. PHARMACEUTICAL FORM

Film-coated tablets

XIFAXAN

Pink oval biconvex film-coated tablets embossed with RX on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

XIFAXAN, in addition to lactulose, is indicated for the reduction in recurrence of episodes of overt hepatic encephalopathy in patients ≥ 18 years of age (see "Pharmacodynamic properties").

4.2 Posology and method of administration

Posology

Recommended dose: 550 mg twice a day. The clinical benefit was established from a controlled study in which subjects were treated for 6 months. Safety and efficacy have not been proven beyond 6 months.

XIFAXAN should be used with appropriate lactulose dosages.

Paediatric population

The safety and efficacy of XIFAXAN in paediatric patients (aged less than 18 years) have not been established.

Elderly

No dosage adjustment is necessary as the safety and efficacy data of XIFAXAN showed no differences between the elderly and the younger patients.

Hepatic impairment

No dosage adjustment is necessary for patients with hepatic insufficiency (see section 4.4)

Renal impairment

Although dosing change is not anticipated, caution should be used in patients with impaired renal function (see section 5.2)

Method of administration

Orally with a glass of water

XIFAXAN can be administered with or without food.

4.3 Contraindications

- Hypersensitivity to rifaximin, rifamycin-derivatives or to any of the other excipients listed in section 6.1.
- Bowel obstruction

4.4 Special warnings and precautions for use

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including rifaximin. The potential association of rifaximin treatment with CDAD and pseudomembranous colitis (PMC) cannot be ruled out.

Due to the lack of data and the potential for severe disruption of gut flora with unknown consequences, concomitant administration of XIFAXAN with other rifamycins is not recommended.

Patients should be informed that despite the negligible absorption of the medicine (less than 1 %), like all rifamycin derivatives, XIFAXAN may cause a reddish discolouration of the urine.

Hepatic impairment: use with caution in patients with severe (Child-Pugh C) hepatic impairment and in patients with MELD (Model for End-Stage Liver Disease) score > 25 (see section 5.2).

Caution should be exercised when concomitant use of XIFAXAN and a P-glycoprotein inhibitor such as cyclosporin is needed (see section 4.5).

Both decreases and increases in international normalized ratio (in some cases with bleeding events) have been reported in patients maintained on warfarin and prescribed XIFAXAN. If co-administration is necessary, the international normalized ratio should be carefully monitored with the addition or withdrawal of treatment with XIFAXAN. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see section 4.5).

4.5 Interaction with other medicines and other forms of interaction

There is no experience regarding administration of XIFAXAN to subjects who are taking another rifamycin antibacterial agent to treat a systemic bacterial infection.

In vitro data show that XIFAXAN did not inhibit the major cytochrome P-450 (CYP) drug metabolizing enzymes (CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4). In *in vitro* induction studies, XIFAXAN did not induce CYP1A2 and CYP2B6 but was a weak inducer of CYP3A4.

In healthy subjects, clinical medicine interaction studies demonstrated that XIFAXAN did not significantly affect the pharmacokinetics of CYP3A4 substrates, however, in hepatic impaired patients it cannot be excluded that XIFAXAN may decrease the exposure of concomitant CYP3A4 substrates administered (e.g. warfarin, antiepileptics, antiarrhythmics, oral contraceptives), due to the higher systemic exposure with respect to healthy subjects.

Both decreases and increases in international normalized ratio have been reported in patients maintained on warfarin and prescribed XIFAXAN. If co-administration is necessary, the international normalized ratio should be carefully monitored with the addition or withdrawal of XIFAXAN. Adjustments in the dose of oral anticoagulants may be necessary.

An *in vitro* study suggested that rifaximin is a moderate substrate of P-glycoprotein (P-gp) and metabolized by CYP3A4. It is unknown whether concomitant medicines which inhibit CYP3A4 can increase the systemic exposure of rifaximin.

In healthy subjects, co-administration of a single dose of ciclosporin (600 mg), a potent P-glycoprotein inhibitor, with a single dose of XIFAXAN (550 mg) resulted in 83-fold and 124-fold increases in rifaximin mean C_{max} and AUC∞. The clinical significance of this increase in systemic exposure is unknown.

The potential for interactions to occur at the level of transporter systems has been evaluated *in vitro* and these studies suggest that a clinical interaction between XIFAXAN and other compounds that undergo efflux via P-gp and other transport proteins is unlikely (MRP2, MRP4, BCRP and BSEP).

4.6 Fertility, pregnancy and lactation

Pregnancy

XIFAXAN should not be used during pregnancy.

There is no or limited data from the use of XIFAXAN in pregnant women.

Animal studies showed transient effects on ossification and skeletal variations in the foetus (see section 5.3).

As a precautionary measure, use of XIFAXAN during pregnancy is not recommended.

Lactation

It is unknown whether rifaximin/metabolites are excreted in human milk.

A risk to the breast-fed child cannot be excluded.

XIFAXAN should not be used by women breastfeeding their infants.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to male and female fertility.

4.7 Effects on ability to drive and use machines

Dizziness has been reported in clinical controlled trials.

Patients should be warned that dizziness may impair their ability to drive or use machines.

4.8 Undesirable effects

Adverse reactions that occurred in patients treated with rifaximin at an incidence ≥ 5 % and at a higher incidence (≥ 1 %) than placebo patients in RFHE3001 are reported in the following table.

Table 1: Adverse reactions occurring in ≥ 5 % of patients receiving rifaximin and at a higher incidence than placebo in RFHE3001

MeDRA System Organ Class	**Event**	**Placebo N = 159**		**Rifaximin N = 140**	
		n	**%**	**n**	**%**
Blood and lymphatic system disorders	Anaemia	6	3,8	11	7,9
Gastrointestinal disorders	Ascites	15	9,4	16	11,4
	Nausea	21	13,2	20	14,3
	Abdominal pain upper	8	5,0	9	6,4
General disorders and administration site conditions	Oedema peripheral	13	8,2	21	15,0
	Pyrexia	5	3,1	9	6,4
Musculoskeletal and connective tissue disorders	Muscle spasms	11	6,9	13	9,3
	Arthralgia	4	2,5	9	6,4
Nervous system disorders	Dizziness	13	8,2	18	12,9
Psychiatric disorders	Depression	8	5,0	10	7,1

Respiratory, thoracic and mediastinal disorders	Dyspnoea	7	4,4	9	6,4
Skin and subcutaneous tissue disorders	Pruritus	10	6,3	13	9,3
	Rash	6	3,8	7	5,0

Table 2 includes adverse reactions observed in the placebo-controlled study RFHE3001, long term study RFHE3002 and from post-marketing experience, listed by MedDRA system organ class and frequency category.

Frequency categories are defined using the following convention:

Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000), Not known (frequency cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Adverse reactions listed by MedDRA system organ class and frequency category

MedDRA System Organ Class	**Common**	**Uncommon**	**Rare**	**Not known**
Infections and infestations		Clostridial infection, urinary tract infection, candidiasis	Pneumonia, cellulitis, upper respiratory tract infections, rhinitis	
Blood and lymphatic system disorders		Anaemia		Thrombocytopenia
Immune system disorders				Anaphylactic reactions, angioedemas, hypersensitivity
Metabolism and nutrition disorders		Anorexia, hyperkalaemia	Dehydration	

Psychiatric disorders	Depression	Confusional state, anxiety, hypersomnia, insomnia		
Nervous system disorders	Dizziness, headache	Balance disorders, amnesia, convulsion, attention disorders, hypoesthesia, memory impairment		
Vascular disorders		Hot flush	Hypertension, hypotension	Presyncope, syncope
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Pleural effusion	Chronic obstructive pulmonary disease	
Gastro-intestinal disorders	Abdominal pain upper, abdominal distension, diarrhoea, nausea, vomiting, ascites	Abdominal pain, oesophageal varices haemorrhage, dry mouth, stomach discomfort	Constipation	
Hepatobiliary disorders				Liver function tests abnormalities
Skin and subcutaneous tissue disorders	Rashes, pruritus			Dermatitis, eczema

Musculo-skeletal and connective tissue disorders	Muscle spasms, arthralgia	Myalgia	Back pain	
Renal and urinary disorders		Dysuria, pollakiuria	Proteinuria	
General disorders and administration site conditions	Peripheral oedema	Oedema, pyrexia	Asthenia	
Investigations				International normalised ratio abnormalities
Injury, poisoning and procedural complications		Fall	Contusions, procedural pain	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of XIFAXAN is important. It allows continued monitoring of the benefit/risk balance of XIFAXAN. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

No case of overdose has been reported.

In case of accidental overdose, symptomatic treatment and supportive care are suggested.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Intestinal, anti-infective - antibiotics, ATC code: A07AA11.

Mechanism of action

Rifaximin is an antibacterial medicine of the rifamycin class. It irreversibly binds the beta sub-unit of the bacterial enzyme DNA-dependent RNA polymerase and consequently inhibits bacterial RNA synthesis.

Rifaximin has a broad antimicrobial spectrum against most of the Gram-positive and negative, aerobic and anaerobic bacteria, including ammonia producing species. Rifaximin may inhibit the division of urea-deaminating bacteria, thereby reducing the production of ammonia and other compounds that are believed to be important to the pathogenesis of hepatic encephalopathy.

Mechanism of resistance

The development of resistance to rifaximin is primarily a reversible chromosomal one-step alteration in the *rpoB* gene encoding the bacterial RNA polymerase.

Experimental and clinical data suggest that the treatment with rifaximin of patients harbouring strains of *Mycobacterium tuberculosis* or *Neisseria meningitidis* will not select for rifampicin resistance.

Susceptibility

Rifaximin is a non-absorbed antibacterial agent. *In vitro* susceptibility testing cannot be used to reliably establish susceptibility or resistance of bacteria to rifaximin. There are currently insufficient data available to support the setting of a clinical breakpoint for susceptibility testing.

Rifaximin has been evaluated *in vitro* on several pathogens including ammonia producing bacteria as *Escherichia coli* spp, *Clostridium* spp, *Enterobacteriaceae*, *Bacteroides* spp. Due to the very low absorption from the gastrointestinal tract rifaximin is not clinically effective against invasive pathogens, even though these bacteria are susceptible *in vitro*.

5.2 Pharmacokinetic properties

Absorption

Pharmacokinetic studies in rats, dogs and humans demonstrated that after oral administration rifaximin in the polymorph α form is poorly absorbed (less than 1 %). After repeated administration of therapeutic doses of rifaximin in healthy volunteers and patients with damaged intestinal mucosa (Inflammatory Bowel Disease),

plasma levels are negligible (less than 10 ng/mL). In hepatic encephalopathy (HE) patients, administration of rifaximin 550 mg twice a day showed mean rifaximin exposure approximately 12-fold higher than that observed in healthy volunteers following the same dosing regimen. A clinically irrelevant increase of rifaximin systemic absorption was observed when administered within 30 minutes of a high-fat breakfast.

Distribution

Rifaximin is moderately bound to human plasma proteins. *In vivo*, the mean protein binding ratio was 67,5 % in healthy subjects and 62 % in patients with hepatic impairment when rifaximin 550 mg was administered.

Biotransformation

Analysis of faecal extracts demonstrated that rifaximin is found as the intact molecule, implying that it is neither degraded nor metabolised during its passage through the gastrointestinal tract.

In a study using radio-labelled rifaximin, urinary recovery of rifaximin was 0,025 % of the administered dose, while < 0,01 % of the dose was recovered as 25-desacetylrifaximin, the only rifaximin metabolite that has been identified in humans.

Elimination

A study with radio-labelled rifaximin suggested that ^{14}C-rifaximin is almost exclusively and completely excreted in faeces (96,9 % of the administered dose). The urinary recovery of ^{14}C-rifaximin does not exceed 0,4 % of the administered dose.

Linearity/non-linearity

The rate and extent of systemic exposure of humans to rifaximin appeared to be characterised by non-linear (dose-dependent) kinetic which is consistent with the possibility of dissolution-rate-limited absorption of rifaximin.

Special populations

Renal impairment

No clinical data are available on the use of rifaximin in patients with impaired renal function.

Hepatic impairment

Clinical data available for patients with hepatic impairment showed a systemic exposure higher than that observed in healthy subjects. The systemic exposure of rifaximin was about 10-, 13-, and 20-fold higher in those patients with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment, respectively, compared to that in healthy volunteers. The increase in systemic exposure to rifaximin in subjects with hepatic impairment should be interpreted in light of rifaximin gastrointestinal local action and its low systemic bioavailability, as well as the available rifaximin safety data in subjects with cirrhosis.

Therefore, no dosage adjustment is recommended because rifaximin is acting locally.

Paediatric population

The pharmacokinetics of rifaximin has not been studied in paediatric patients of any age. Population studied in both the reduction in recurrence of hepatic encephalopathy (HE) and in the acute treatment of HE included patients aged ≥ 18 years.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

In a rat embryofoetal development study, a slight and transient delay in ossification that did not affect the normal development of the offspring, was observed at 300 mg/kg/day (2,7 times the proposed clinical dose for hepatic encephalopathy, adjusted for body surface area). In the rabbit, following oral administration of rifaximin during gestation, an increase in the incidence of skeletal variations was observed (at doses similar to those proposed clinically for hepatic encephalopathy). The clinical relevance of these findings is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients

Tablet core

Sodium starch glycolate type A

Glycerol distearate

Colloidal anhydrous silica

Talc

Microcrystalline cellulose

Film coat (Opadry OY-S-34907)

Hypromellose

Titanium dioxide (E171)

Disodium edetate

Propylene glycol

Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the tablets in the blister strip and the strips in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Transparent, colourless PVC/PE/PVDC silver Aluminium blister strips in cardboard boxes. Each blister strip contains 14 tablets and 4 blister strips per outer carton.

Pack size: 56 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd.

100 Sovereign Drive, Route 21 Corporate Park

Nellmapius Drive, Irene, Pretoria

8. REGISTRATION NUMBER

51/20.1.1/0036

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 JULY 2020

10. DATE OF REVISION OF THE TEXT